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## Summary of Findings from the Audits, Reviews, and Re-Evaluations of the REMIT Trial

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### Background and Overview

The following summarizes the main findings from the audits, reviews, re-analyses, and re-evaluations of the REMIT Trial undertaken at the initial request by the Department of Psychiatry.

The summary is based on the following reports: (1) Duke OARC Internal Audit Report (Dated: 18 Oct 2018); (2) Psychiatry CRU Review (Dated: 22 Dec 2018); (3) DCRI Re-Analysis of REMIT Primary Outcome Manuscript (Dated: 11 April 2019); (4) DCRI Re-Evaluation of REMIT Echocardiography Images (Dated: 12 Sept 2019); and (5) Findings from Faculty Standing Committee (Received by the Psychiatry Department on 12 Dec 2019)

### Findings Regarding Research Misconduct

Regarding the grievous concern of potential scientific falsification or fabrication, the Standing Committee concluded the following:

1. There is insufficient evidence that Dr. Jiang, or any member of her study team, falsified or fabricated in REMIT study records to warrant investigation into the Allegation.
2. There is insufficient evidence that Dr. Jiang, or any member of her study team, falsified or fabricated information in REMIT study publications to warrant investigation into the Allegation.

### Findings Regarding Compliance with Good Clinical Practice (GCP)

Regarding the significant concern of compliance with Good Clinical Practice (GCP), applicable US Food and Drug Administration (FDA) regulatory requirements, and institutional policies and procedures, the 5 reviews found the following:

1. The audits and reviews concluded that the REMIT study was not conducted according to, and hence noncompliant with, the protocol approved by the Duke IRB.
2. The audits and reviews also noted numerous discrepancies between the research record and the approved protocol. Chief among these were:
  - a. Enrolling and randomizing 26 research participants who did not meet inclusion or exclusion criteria (e.g., enrolling subjects who could not complete the baseline exercise stress test)

- b. Inconsistent adherence to study protocol (e.g., failure to withhold antianginals prior to stress testing; failure to blind MD Echo readers to which visit they were reading).
  - c. Conducting study procedures that were not part of approved protocol and not specified in the consent documentation (e.g., publishing on participants who only completed the baseline assessment).
- 3. The audits and reviews found that Dr. Jiang failed to inform the IRB regarding protocol changes made during the course of trial.
- 4. The audits and reviews found that Dr. Jiang failed to secure IRB approval before implementing protocol changes.
- 5. The audits and reviews noted poor regulatory oversight by Dr. Jiang.
- 6. The audits and reviews noted many instances of poor, incomplete, and inconsistent study documentation.
- 7. Findings from the re-analyses of the data and re-evaluations of the mental and exercise stress assessments also noted that the protocol was ambiguous with respect to the definition of the primary endpoint and its calculation.
- 8. The Standing Committee also noted that reporting of the REMIT study methods and outcomes in the two main publications (2012 *Am Heart J*; 2013 *JAMA*) does not accurately reflect the research record. Discrepancies between the research recorded and study publications resulted from Dr. Jiang's view that the primary focus of the REMIT study was mental stress testing and MSIMI evaluation, which is not consistent with the approved study protocol.

#### **Findings Regarding the Statistical Reanalysis of the REMIT JAMA Primary Outcome Paper**

Faculty and staff from Biostatistics at DCRI were asked to conduct a re-analysis of the REMIT primary outcome paper to (1) replicate the findings reported in the primary publication using the same datasets created for the primary outcome paper and (2) to evaluate how the results might change if the participants who did not meet inclusion criteria were removed from the analyses. These re-analyses were conducted using the same methods reported in the primary outcome paper. The main findings from this review are as follows:

- 1. The results from the replication analyses found that most of the discrepancies between what was published in the primary outcome paper were minor suggesting some carelessness in the reporting of the main findings. The overall substantive conclusions remain the same.

2. Results from the re-analyses removing participants who were identified as not meeting inclusion or exclusion criteria were significantly changed. With the reduced population, the lower rate of MSIMI at endpoint in escitalopram participants does not reach statistical significance and the magnitude of the effect is attenuated. The odds ratio for the association between escitalopram treatment and no MSIMI was published to be 2.68 in completers (2.62 when imputed) and in the reduced sample outcomes the odds ratio was reduced to 1.99 (1.97 when imputed). P-values that were less than 0.05 in the JAMA publication are greater than 0.1 in the subset deemed eligible.

#### **Department of Psychiatry and Committee Factors Contributing to Research Noncompliance**

The Standing Committee and Department of Psychiatry leadership noted the following factors contributing to Dr. Jiang's research noncompliance:

1. Dr. Jiang's lack of experience conducting clinical trials.
3. Dr. Jiang's inattention to detail.
4. A clear discrepancy between Dr. Jiang's understanding of the study and the description of the study provided in the protocol.
5. Insufficient time and resources to accurately document and report study findings.
6. Turn-over amongst staff and limited funding to properly train study personnel.

#### **Department Decision**

1. In conjunction with departmental leadership, Dr. Jiang must contact the managing editors of the two main publications to determine if corrections and/or retractions to the publications are warranted.
2. In conjunction with departmental leadership, Dr. Jiang, and appropriate co-authors, must review the other REMIT publications to determine whether the research is accurately represented and/or if the managing editors of the journals need to be contacted about corrections and/or retractions.
3. Effective immediately, per the Chair, Dr. Moira Rynn, Dr. Jiang is no longer approved to propose, submit, or participate in new research related effort as a faculty member of the Department of Psychiatry and Behavioral Sciences at Duke University.
4. All effort on existing research as Principal Investigator or any other research related effort across Duke Health must end as of June 30, 2020.

# REMIT Publications

Note: This list may not be exhaustive.

Contact Managing Editor	Reference
Y <input type="checkbox"/> N <input type="checkbox"/>	1. Jiang W. Response to the "Clarification of the REMIT Trial Protocol". Am Heart J. 2012;164(5): e17. Epub 2012/11/10.
Y <input type="checkbox"/> N <input type="checkbox"/>	2. Jiang W, Velazquez EJ, Samad Z, Kuchibhatla M, Martsberger C, Rogers J, Williams R, Kuhn C, Ortel TL, Becker RC, Pristera N, Krishnan R, O'Connor CM. Responses of mental stress-induced myocardial ischemia to escitalopram treatment: background, design, and method for the Responses of Mental Stress Induced Myocardial Ischemia to Escitalopram Treatment trial. Am Heart J. 2012;163(1):20-6. Epub 2011/12/17. doi: 10.1016/j.ahj.2011.09.018. PubMed PMID: 22172432; PMCID: PMC3254211.
Y <input type="checkbox"/> N <input type="checkbox"/>	3. Boyle SH, Samad Z, Becker RC, Williams R, Kuhn C, Ortel TL, Kuchibhatla M, Prybol K, Rogers J, O'Connor C, Velazquez EJ, Jiang W. Depressive symptoms and mental stress-induced myocardial ischemia in patients with coronary heart disease. Psychosom Med. 2013;75(9):822-31. Epub 2013/10/29. doi: 10.1097/PSY.0b013e3182a893ae. PubMed PMID: 24163385; PMCID: PMC4378828.
Y <input type="checkbox"/> N <input type="checkbox"/>	4. Jiang W, Samad Z, Boyle S, Becker RC, Williams R, Kuhn C, Ortel TL, Rogers J, Kuchibhatla M, O'Connor C, Velazquez EJ. Prevalence and clinical characteristics of mental stress-induced myocardial ischemia in patients with coronary heart disease. J Am Coll Cardiol. 2013;61(7):714-22. Epub 2013/02/16. doi: 10.1016/j.jacc.2012.11.037. PubMed PMID: 23410543; PMCID: PMC3913125.
Y <input type="checkbox"/> N <input type="checkbox"/>	5. Jiang W, Velazquez EJ, Kuchibhatla M, Samad Z, Boyle SH, Kuhn C, Becker RC, Ortel TL, Williams RB, Rogers JG, O'Connor C. Effect of escitalopram on mental stress-induced myocardial ischemia: results of the REMIT trial. JAMA. 2013;309(20):2139-49. Epub 2013/05/23. doi: 10.1001/jama.2013.5566. PubMed PMID: 23695483; PMCID: PMC4378823.
Y <input type="checkbox"/> N <input type="checkbox"/>	6. Ersboll M, Al Enezi F, Samad Z, Sedberry B, Boyle SH, O'Connor C, Jiang W, Velazquez EJ, Investigators R. Impaired Resting Myocardial Annular Velocities Are Independently Associated With Mental Stress-Induced Ischemia in Coronary Heart Disease. Jacc-Cardiovasc Imag. 2014;7(4):352-61. doi: DOI 10.1016/j.jcmg.2013.10.014. PubMed PMID: WOS:000335093500003.
Y <input type="checkbox"/> N <input type="checkbox"/>	7. Samad Z, Boyle S, Ersboll M, Vora AN, Zhang Y, Becker RC, Williams R, Kuhn C, Ortel TL, Rogers JG, O'Connor CM, Velazquez EJ, Jiang W, Investigators R. Sex differences in platelet reactivity and cardiovascular and psychological response to mental stress in patients with stable ischemic heart disease: insights from the REMIT study. J Am Coll Cardiol. 2014;64(16):1669-78. Epub 2014/10/18. doi: 10.1016/j.jacc.2014.04.087. PubMed PMID: 25323254; PMCID: PMC4752118.

Y <input type="checkbox"/> N <input type="checkbox"/>	8. Boyle SH, Matson WR, Velazquez EJ, Samad Z, Williams RB, Sharma S, Thomas B, Wilson JL, O'Connor C, Jiang W. Metabolomics analysis reveals insights into biochemical mechanisms of mental stress-induced left ventricular dysfunction. <i>Metabolomics</i> . 2015;11(3):571-82. doi: 10.1007/s11306-014-0718-y. PubMed PMID: WOS:000354137100006.
Y <input type="checkbox"/> N <input type="checkbox"/>	9. Jiang W, Boyle SH, Ortel TL, Samad Z, Velazquez EJ, Harrison RW, Wilson J, Kuhn C, Williams RB, O'Connor CM, Becker RC. Platelet aggregation and mental stress induced myocardial ischemia: Results from the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) study. <i>Am Heart J</i> . 2015;169(4):496-507 e1. Epub 2015/03/31. doi: 10.1016/j.ahj.2014.12.002. PubMed PMID: 25819856; PMCID: PMC4382806.
Y <input type="checkbox"/> N <input type="checkbox"/>	10. Alenezi F, Brummett BH, Boyle SH, Samad Z, Babyak MA, Alzaeim N, Wilson J, Romano MMD, Sun JL, Ersboll M, O'Connor CM, Velazquez EJ, Jiang W. Usefulness of Myocardial Annular Velocity Change During Mental Stress to Predict Cardiovascular Outcome in Patients With Coronary Artery Disease (From the Responses of Mental Stress-Induced Myocardial Ischemia to Escitalopram Treatment Trial). <i>Am J Cardiol</i> . 2017;120(9):1495-500. Epub 2017/09/18. doi: 10.1016/j.amjcard.2017.07.039. PubMed PMID: 28917493.
Y <input type="checkbox"/> N <input type="checkbox"/>	11. Feigal JP, Boyle SH, Samad Z, Velazquez EJ, Wilson JL, Becker RC, Williams RB, Kuhn CM, Ortel TL, Rogers JG, O'Connor CM, Jiang W. Associations between positive emotional well-being and stress-induced myocardial ischemia Well-being scores predict exercise-induced ischemia. <i>J Psychosom Res</i> . 2017;93:14-8. doi: 10.1016/j.jpsychores.2016.11.012. PubMed PMID: WOS:000393270900003.
Y <input type="checkbox"/> N <input type="checkbox"/>	12. Feigal JP, Boyle SH, Samad Z, Velazquez EJ, Wilson JL, Becker RC, Williams RB, Kuhn CM, Ortel TL, Rogers JG, O'Connor CM, Jiang W. Associations between positive emotional well-being and stress-induced myocardial ischemia Well-being scores predict exercise-induced ischemia. <i>J Psychosom Res</i> . 2017;93:14-8. doi: 10.1016/j.jpsychores.2016.11.012. PubMed PMID: WOS:000393270900003.
Y <input type="checkbox"/> N <input type="checkbox"/>	13. Sun JL, Boyle SH, Samad Z, Babyak MA, Wilson JL, Kuhn C, Becker RC, Ortel TL, Williams RB, Rogers JG, O'Connor CM, Velazquez EJ, Jiang W. Mental stress-induced left ventricular dysfunction and adverse outcome in ischemic heart disease patients. <i>Eur J Prev Cardiol</i> . 2017;24(6):591-9. doi: 10.1177/2047487316686435. PubMed PMID: WOS:000397435200004.

